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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/924,944 | 08/08/2001 | Douglas C. Harnish | 0630/1G704US2 | 2000 |

23483 7590 08/10/2005

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| EXAMINER | |
|---|---|
| YU, MISOOK | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/924,944 | HARNISH ET AL. | |
| | Examiner | Art Unit | |
| | MISOOK YU, Ph.D | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *12-24 and 26-42* is/are pending in the application.

4a) Of the above claim(s) *12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 12-24 remain withdrawn for reason of record. Claims 12-24, and 26-42 are pending. Claims 26-44 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112, Withdrawn*

The rejection of claims 35, and 39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention I withdrawn in view of the amendment

The rejection of claims 26-39 under 35 U.S.C. 112, first paragraph, scope of enablement is also withdrawn in view of the amendment.

The rejection of claims 26-40 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is also withdrawn because the specification originally filed at the paragraph bridging pages 4-5 has the support as applicant points out.

### *Claim Rejections - 35 USC § 103, Maintained*

Claims 26, 27, and 30-40 are under 35 U.S.C. 103(a) as being unpatentable over Calkhoven et al (1997, Eur. J. Biochem. vol. 249, pages 113-120) in view of Ameis et al., of record (1990, J. Biol. Chem. vol. 265, pages 6552-5), further in view of Norris et al., of record (J. Biol. Chem., vol. 270, pages 22777-82).

Claims 26, 27, and 30-40 are interpreted as drawn to recombinant cell (more specifically a hepatocarcinoma cell, i.e., HepG2 cell containing 3 DNA constructs, i.e. 1)

DNA construct expressing a estrogen receptor (more specifically human estrogen receptor alpha (ER-alpha); 2) DNA construct expressing a transcription coactivator C/EBP; 3) a reporter construct linking various art-known reporters listed in claim 33 (more specifically luciferase in claim 34) to hepatic lipase promoter/enhancer that contains CCAAT element (more specifically –1557 to +43 of human HL gene in claim 32), wherein the DNA constructs of the base claim 26 are in the various art-known vectors (pET), wherein claim 40 is drawn to an assay system containing the recombinant cell of the claim 26 for screening useful compounds affecting the ERalpha and/or C/EBP dependent transcription activation of hepatic lipase promoter/enhancer in multi-well format capable of detecting the reporter being used. In summary, the claims are drawn to a recombinant cell per se with 3 exogenous nucleic acid molecules encoding two proteins i.e. a known reporter protein controlled by a HL promoter, a coactivator of transcription (estrogen receptor), and transcription enhancer binding protein of C/EBP.

Applicant argues that Calkhoven et al., do not teach, suggest, and/or motivate one of ordinary skill to substitute the reporter construct linking CAT reporter gene to nucleic acid element that the transcription coactivator C/EBP and ER bind to (i.e. the apoVLDL III promoter) of Calkhoven et al., with HL promoter linked to a reporter taught by Ameis et al. Applicant argues that Calkhoven et al., have no interest in HL promoter, and such substitution would mess up the study purpose of Calkhoven et al. Applicant further argues that the disclosure of Ameis et al., do not enable one of ordinary skill because the HL promoter activity is not disclosed.

These arguments have been fully considered but found unpersuasive. As stated in the previous Office action, Calkhoven et al., at page 116, right column, the last paragraph, Fig. 5B, and Fig. 6 (page 118) teach HepG2 recombinant cells containing 3 DNA constructs, i.e. 1) DNA construct expressing a estrogen receptor expressing a estrogen receptor; 2) DNA construct expressing a transcription coactivator C/EBP in pET expression vector (note under the heading "Expression plasmid" at page 114); 3) a reporter construct linking CAT reporter gene to nucleic acid element that the transcription coactivator C/EBP and ER bind to (i.e. the apoVLDL III promoter). Calkhoven et al., teach that C/EBP and estrogen receptor work together to express

Calkhoven et al., do not teach HL promoter or a luciferase reporter gene.

However, Ameis et al., at Fig. 3 (page 6554), and page 6555, left column, 1st paragraph teach that the human HL promoter contains "two CCAAT elements", and also Alu DNA repeats are present in 5' untranslated region of the human HL gene.

Norris et al., are cited to show that one of ordinary skill in the art would be motivated to screen ER responsive enhancer using a luciferase reporter gene. Norris et al., teach "estrogen is a key intracellular modulator" including "female cardiovascular tone" (note 1st sentence at page 22777), and also teach that "[b]ecause of its diverse biological functions and the implied complexity of its targets, there has been keen interest in defining the genes which are regulated by estrogen" (note 1st sentence of right column at page 22777), and also teach that the Alu consensus sequence (i.e. GGTCANNNTGGTCNNNNNNNNTCACC) that ER binds to as shown at Fig. 4 (page 22781), and also teach an assay system using luciferase at page 22778.

In summary, reviewing sequence of HL promoter disclosed by Ameis et al., "the hepatic lipase promoter is positioned proximal to the 5'end of human hepatic lipase coding region" as claimed in the instant claim 31, or "the hepatic lipase promoter comprises human hepatic lipase promoter region from –1557 to + 43, relative to the human hepatic coding region start site" as claimed in the instant claim 32 contains the consensus ER binding Alu site and the consensus CCAAT sites that C/EBP protein binds to.

In response to applicant's arguments against the references individually (i.e. primary reference does not specifically pointing out the HL promoter) , one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As for Ameis being not enabling disclosure to be used as a promoter, the Office cites a new reference, i.e. a textbook published in 1990 more than 20 years before the effective filing date of the instant application by Voet et al., (1990, John Wiley & Sons, page 865 only) teach that CCAAT sites disclosed by Ameis et al., is a classic promoter element. Thus, one of ordinary skill at the time the instant application was filed would have believed that HL promoter disclosed by Ameis et al., would work as a promoter and one of ordinary skill would have been able to use the HL promoter disclosed by Ameis et al., with a reasonable expectation of success given undergraduate students had been taught a promoter containing CCAAT sites would work 20 years before the effective filing date of the instant application.

Therefore, it would have been obvious to one of ordinary skill to make and use a recombinant cells containing the claimed 3 different DNA constructs with a reasonable expectation of success by taking out the replacing the apoVLDL II promoter of the reporter construct of Calkhoven et al., with the HL promoter of Ameis et al., to arrive at an estrogen-dependent HL promoter-driven reporter gene. The skill in the art in making the claimed recombinant cell using a known nucleic acid sequence is very high. One of ordinary skill would be motivated to make and use an estrogen-dependent HL promoter-driven reporter gene given that the Alu repeat of the HL promoter at its 5' untranslated region (note at Fig. 3 legend of Ameis et al.) contains the consensus Alu consensus sequence (i.e. *GGTCA*NNNT*GGTC*NNNNNNNN*TGACC*) that ER binds to as shown at Fig. 4 of Norris et al., (page 22781). In other words, the sequence of *ggtca*-ggc-*tggtc*-tcgaactcc-*tgacc* located between –1057 and –957 of Fig. 3 of Ameis et al., belongs to the Alu consensus sequence for ER binding. One of ordinary skill would have been motivated to make and use the claimed recombinant cell for screening compounds regulating the hepatic lipase gene promoter, which contains both the ER responsive element, and C/EBP element since Norris et al., suggest that regulating ER responsive gene would be a good target in heart diseases and other lipid-metabolism-related diseases in women.

Claims 26-28 are under 35 U.S.C. 103(a) as being unpatentable over Calkhoven et al (1997, Eur. J. Biochem. vol. 249, pages 113-120) in view of Ameis et al., of record (1990, J. Biol. Chem. vol. 265, pages 6552-5), further in view of Norris et al., of record

(J. Biol. Chem., vol. 270, pages 22777-82), and further in view of Harnish et al., of record (1998, J. Biol. Chem., vol. 273, pages 9270-8).

Claims 26-28 are interpreted as drawn to a recombinant cell per se with 3 exogenous nucleic acid molecules encoding two proteins i.e. a known reporter protein controlled by a HL promoter, a estrogen receptor alpha or beta, and transcription enhancer binding protein of C/EBP.

Applicant argues that Calkhoven, and Ameis et al are no good references for the claimed invention, therefore this rejection is no good, either. This argument has fully considered but found unpersuasive for the reasons given above.

Note 103(a) rejection above for what Calhoven et al., Ameis et al., or Morris et al., teach. In summary, combination of Calhoven et al., Ameis et al., or Morris et al., teach recombinant cell per se with 3 exogenous nucleic acid molecules encoding two proteins i.e. a known reporter protein controlled by a HL promoter, a estrogen receptor, and transcription enhancer binding protein of C/EBP.

However, none of Calhoven et al., Ameis et al., or Morris et al., specifically points out estrogen receptor alpha or beta.

However, Harnish et al., at page 9270, right column, last paragraph, 1$^{st}$ line teach that estrogen receptor alpha or beta as claimed in instant claim 28 had been known well before the effective filing date of instant application.

Therefore, it would have been obvious to one of ordinary skill to make and use a recombinant cells containing the claimed 3 different DNA constructs with a reasonable expectation of success by using the known sequence of estrogen receptor alpha or beta

since the skill in the art in making the claimed recombinant cell using a known nucleic acid sequence is very high.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642